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Biomarkers of Renal Injury in Cirrhosis: Association with Acute Kidney Injury and Recovery after Liver Transplantation

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Abstract

Background—To define urine or serum biomarkers in predicting renal function recovery after liver transplantation (LT).

Methods—Adults listed for LT (02/11 – 07/14) and with modified diet for renal disease-6 (MDRD-6) <60 mL/min provided urine/blood samples at baseline and serially until LT for biomarkers in serum (pg/ml) and urine (pg/mg creatinine).

Results—Of 271 LT listed patients (mean age 57 yrs., 63% males, median listing MELD 17.5), one year AKI probability was 49%, with odds of 1.3, 3.0, 4.6, and 8.5 fold for listing MELD 16–20, 21–25, 26–30, and >30, compared to MELD <16. 37 died over 1 year from listing, with 2 fold increased odds with AKI. Among 67 patients with MDRD<60, only urinary epidermal growth factor (EGF) was different comparing AKI (increase in serum creatinine ≥.3 mg/dL from baseline

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within past 3 months) vs. no AKI (2254 vs. 4253, P=0.003). Differences between acute tubular necrosis (ATN) and hepatorenal syndrome could not be ascertained, for small sample of 3 patients with ATN. Analyzing 15 of 43 receiving LT and MDRD-6 <30 prior to LT, biomarkers were not different comparing five patients recovering renal function (MDRD-6 >50 mL/min) at six months vs. 10 without recovery.

Conclusions—AKI is common among LT listed patients, with a negative impact on transplant free survival. Serum and urine biomarkers are not associated with recovery of renal function after LT. Multicenter studies are suggested to a) develop strategies to reduce development of AKI and b) deriving novel biomarkers using to accurately predict renal recovery after LT.

Keywords

Biomarkers; Simultaneous Liver Kidney; AKI; Cirrhosis; ESRD

INTRODUCTION

Acute kidney injury (AKI) occurs commonly in patients with cirrhosis with rates of about 19–49% [1–8], and negatively impacts patient survival before and after liver transplantation (LT) [1, 5, 6, 9–12]. AKI in patients with cirrhosis occurs commonly due to volume loss; hepatorenal syndrome (HRS) due to vasoconstriction and reduced renal blood flow; and acute tubular necrosis (ATN) due to prolonged pre-renal factors, sepsis, or nephrotoxic insults [8, 11, 13–15]. To our knowledge, there are no studies describing AKI among patients with cirrhosis after being listed for liver transplantation (LT).

Routine clinical and laboratory evaluation is often unable to accurately differentiate hepatorenal syndrome (HRS) from intra-renal causes, and renal biopsy is invasive with a potential for complications [7, 8, 16]. AKI secondary to ATN may often require simultaneous liver kidney (SLK) transplantation for renal function recovery. In contrast, AKI due to HRS, usually recovers after liver transplantation (LT) alone. Imperfect criteria for allocating simultaneous liver kidney (SLK) transplantation in the setting of AKI, [17, 18] combined with introduction of MELD score for LT listing [19], have resulted in over 300% increase in SLK transplantation [18, 20]. Given the scarcity of donor kidneys [21], there is a need for biomarkers or models for accurate prediction of renal recovery after LT alone for optimal allocation of donor kidneys.

Biomarkers of renal injury such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interlukin-18 (IL-18), human endothelin-1 (HE-1), uromodulin (UMOD), epidermal growth factor (EGF), fatty acid binding protein (FABP) and many others have been shown to predict recovery of renal function in patients with AKI without liver disease, development of AKI during LT, and differentiating HRS from ATN [10, 22, 23]. However, there are limited data on efficacy of these biomarkers in predicting recovery of renal function after LT alone. We prospectively recruited patients with liver cirrhosis listed for LT with specific aims to a) examine the probability of development of AKI and its impact on waitlist mortality and b) association of levels of serum and urine biomarkers of renal injury with type of AKI before LT and with renal function recovery after LT.

METHODS

Study Population

This is a prospective-retrospective cohort study of adult patients with liver cirrhosis listed for LT between 02/2011 and 07/2014 (Figure 1). Patients with prior liver or kidney transplant were excluded. The prospective cohort included cirrhosis patients listed for LT between April 2013 and July 2014, and were recruited after informed consent in an ongoing prospective longitudinal study to define urine and serum biomarkers in predicting recovery of renal function after LT. The retrospective cohort included patients listed between February 2011 and the recruitment of prospective study cohort starting April 2013. Both cohorts were followed until the data cut-off date of December 2015. Medical charts were reviewed to obtain prospective follow up data on the retrospective cohort. The study was approved by our institutional review board. Study was conducted adhering to the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Study Outcomes

One year probability of AKI and of patient survival after LT listing.

Collection of Urine and Serum Samples

A subgroup of patients with MDRD-6 <60 mL/min. of the prospective cohort were consented to provide 50 mL urine and 10 mL blood samples at recruitment and then every future encounter in outpatient or during inpatient admission, until LT or removal from the waitlist. Patients receiving LT alone were followed for six months to measure their renal function and assess recovery of renal function. Patients receiving SLK transplantation were excluded from the analysis (Figure 1). Please see Supplementary material methods section for details on data collection, definitions, measurement of serum and urine biomarkers, and statistical analyses approach.

RESULTS

Study Population

A total of 271 patients (median age 56 years, 63% males, 83% Caucasians, median MDRD-6 and MELD score at listing of 66 mL/min and 18 respectively) meeting eligibility criteria for the study were analyzed (Table 1). Pre-existent CKD was present in 64 (24%) patients, which was due to diabetes in 31 patients. Common causes of liver cirrhosis were hepatitis C virus infection, non-alcoholic steatohepatitis, and alcohol use in 100 (37%), 72 (27%), and 36 (13%) patients respectively. Of 100 patients with HCV infection, 44 had received treatment for this disease. A total of 230 (85%) patients had decompensated disease with either presence of ascites or hepatic encephalopathy or varices (Table 1).

Of the prospective cohort, 70 patients (mean age 58 yrs., 54% males, 84% Caucasians) with MDRD-6 <60 (median 37 mL/min) were recruited to provide serum and urine samples for biomarkers measurements (Supplementary Figure 1 and Supplementary Table 1). About half

of these patients had underlying CKD (10% on hemodialysis, due to associated comorbidities of diabetes mellitus in 49% and hypertension in 46% (Table 1). Of 7 patients on hemodialysis at the time of inclusion into the study, 3 were receiving this for ESRD (all these receiving SLK transplantation and were excluded from the analysis on biomarkers), and remaining four were initiated on dialysis for AKI.

A total of 242 samples were collected from 70 patients from the time of recruitment until removal from the transplant list, with 131 serum samples from 69 patients and 111 urine samples from 65 patients (Supplementary Figure 1). A total of 35 and 37 patients provided only the baseline serum or urine sample, and 22 and 18 patients provided two serum or urine samples. The remaining patients provided more than two samples with maximum of five serum samples by each of the two patients and six urine samples by one patient (Supplementary Figure 1).

Probability of Acute Kidney Injury

Over a median (interquartile range) follow up period of 1.43 (0.85–2.17) years, 107 of 271 (39.5%) patients developed first episode of AKI, with one year probability of 49% (Figure 2A). Similar probabilities at listing MELD score <16 (N=95), 16–20 (N=100), 21–25 (N=33), 26–30 (N=19), and >30 (N=24) were 31.9%, 42.8%, 73.7%, 72.8%, and 91.7% respectively (Log Rank P<0.0001, Supplementary Figure 2). Of 107 first AKI episodes, volume responsive pre-renal was the most common etiology of AKI in 61 (57%) patients followed by ATN in 28 (27%), HRS in 10 (9%), and miscellaneous causes in 8 (7%) patients including post-renal etiology in two patients (Supplementary Figure 3). Patients with AKI (N=107) compared to 164 patients without AKI were more likely to have pre-existing CKD, more likely to have refractory ascites and hepatic hepatic encephalopathy, less likely to have hepatocellular carcinoma (HCC), and had lower listing MDRD-6 and serum sodium, and higher MELD score (Table 1). The two groups were no different on decompensated disease (82 vs. 89%, P=0.15) and on varices and platelet count (Table 1). The proportion of patients receiving treatment for HCV infection was also similar in the two groups at 44% (27 of 62) vs. 45% (17 of 38), P=0.91.

Predictors of Acute Kidney Injury

On a cox proportional hazard regression analysis model, MELD score and serum sodium at listing independently predicted development of AKI at one year, with 3 point increase in MELD score increasing the risk by 39% (Supplementary Table 2). Cox regression model built with MELD score as a categorical variable, showed AKI risk at one year from listing to increase linearly by 335%, 399%, and 1223% respectively for listing MELD score of 21–25, 26–30, and >30 respectively, compared to MELD score <15 (Supplementary Table 2).

Impact of Acute Kidney Injury on Waitlist Mortality

A total of 73 (27%) patients died while waiting for LT, higher among patients with AKI (33.6 vs. 12.2%, P=0.0001). Of 73 deaths on waitlist, 37 occurred within first year from listing (21 among patients with AKI). One year probability of survival from listing for LT was about 86%, lower in patients with AKI (72.2% vs. 83%, P=0.025, Figure 3). After controlling for demographics (age and gender), diabetes, obesity, and listing MELD score,

development of AKI increased risk for waitlist mortality at one year from listing by over two-fold: HR (95% CI) of 2.27 (1.28–4.02, P=0.005, Supplementary Table 3). Within the group of 107 patients with AKI, cox proportion hazard regression analysis was built again. Recurrent AKI was not a predictor of waitlist mortality, 0.89 (0.39–2.02, P=0.79). Significant predictors were MELD at listing 1.07 (1.03–1.12, P=0.002) and obesity 1.82 (1.09–3.01, P=0.02).

A total of 145 of 271 (54%) patients were transplanted during the study period, with 8 (2.96% of both the cohorts and 5.5% of all LT) receiving SLK. Proportion of patients receiving LT was similar comparing patients with and without AKI (49% vs. 53%, P=0.47, Supplemental Figure 4). MDRD-6 was consistently lower among patients with AKI at listing, and then at 3 months, 6 months, and 12 months from listing, compared to patients without AKI However, patients surviving the AKI episode without LT return their MDRD-6 to baseline (median MDRD-6 around 60–65 mL/min, Supplementary Figure 5).

Recurrent Acute Kidney Injury

A total of 147 episodes of AKI developed in 107 patients, 27 with two AKI episodes, 12 with three episodes, and one patient had more than three episodes (Supplementary Figure 3). The etiology of recurrent AKI was similar to the proportion of etiologies in the first episode (Supplementary Figure 3). Of 107 patients with first AKI episode, 2nd AKI occurred in 26 (24%) patients among LT free survivors, with one year probability of 60% (Figure 2B). Respective cumulative probabilities for second episode of AKI were 25%, 30%, and 21% among patients with listing MELD <21, 21–25, and >25 compared to MELD<20.

Biomarker Analysis

a) MDRD-6 >30 vs. ≤30 mL/min—Of 122 samples, 34 samples with MDRD-6 ≤30 (median 23 mL/min) compared to 88 samples with MDRD-6 >30 (median 51 mL/min) had significantly higher serum HE-1 and NGAL levels (Supplementary Table 4 and Figure 4 A–B). On urine biomarkers analysis, EGF and IL-18 were significantly lower for samples with MDRD-6 ≤30 (Supplementary Table 4 and Figure 4 C–D). Other biomarkers were not significantly different comparing the two strata of MDRD-6 (Supplementary Table 4).

b) AKI vs. no AKI—Of 134 samples, 37 samples with adjudication of AKI at the time of sample collection compared to 97 samples without AKI had significantly higher serum NGAL and a trend for higher HE-1 levels (Table 2 and Figure 4 E–F). On urine biomarkers analysis, only EGF was significantly different with lower levels for samples with AKI (Table 2 and Figure 4G). Other biomarkers were not significantly different comparing the two strata of MDRD-6 (Table 2).

c) Type of AKI—Of 37 samples with AKI, cause of AKI was pre-renal in 22, HRS in 12, and ATN in three patients. Compared to pre-renal AKI, serum NGAL was higher in ATN and serum HE-1 was higher in HRS (Table 3). However, statistical comparison could not be derived for comparing ATN and HRS with only 3 observations with AKI due to ATN (Table 3).

d) CKD vs. no CKD—Of 134 samples, 62 samples from patients with CKD (median MDRD-6 of 34 mL/min) differed only for urinary EGF, compared to samples obtained from patients without CKD (median MDRD-6 of 51 mL/min) (Supplementary Table 5 and Figure 4B). Further, samples from CKD patients tended to have higher serum NGAL and urinary albumin (Supplementary Table 5 and Figure 4A, 4C).

e) Recovery of Renal Function after Liver Transplantation Alone—Of 70 patients recruited into the study, 46 were transplanted until the end of the data collection. Of these, 43 received liver alone (mea age 57 years, 53% males, 84% Caucasians, baseline MDRD-6 of 40 mL/min) and three patients received SLK transplantation (Table 1). About 44% of transplanted patients had underlying CKD, with pre-transplant hemodialysis in one patient (Table 1). Of 43 patients receiving LT alone, 24 patients provided sample within a month prior to LT, and these patients did not differ at baseline from all the transplanted patients (Table 1).

To examine association of serum and urinary biomarkers with recovery of renal function, we focused on 15 patients receiving liver alone with MDRD-6 <30 at the last sample obtained within a month prior to LT. Of these, 5 patients recovered renal function and 10 patients did not recover their renal function, with recovery defined as return of MDRD-6 to >50 at six months after LT. None of the biomarkers in serum and urine on the latest sample available prior to LT were different comparing patients with and without recovery of renal function. There was a trend for higher UMOD among patients showing recovery of renal function compared to patients not recovering renal function at six months after LT (Supplementary Figure 6 A). Other details on pre-transplant variables and post-transplant use of calcineurin inhibitor are provided in Supplementary Table 5.

DISCUSSION

The frequency of AKI in patients with cirrhosis varies between 19–49%, similar to the current study [1–6]. Differences across studies may be due to study population and follow up time. In this study, probability of occurrence of AKI at one year from the time of listing for LT was 49%. In a retrospective study on 82 patients with Child's class C cirrhosis, AKI occurred in about 23% patients over one year period [24]. In another study, the incidence of AKI was 18% at one year among hospitalized patients with cirrhosis [25]. AKI in cirrhosis is most commonly due to volume responsive prerenal injury followed by ATN and type 1 HRS, similar to what we found in the current study [7, 8, 11, 14, 15].

Biomarkers such as NGAL, KIM-1, IL-18, and FABBP-2 can diagnose AKI earlier, differentiate ATN from HRS, and predict outcomes [22, 23, 26–31]. Of these, serum NGAL and urinary IL-18 were different in this study. Our study population with MDRD-6 <60 and presence of underlying CKD probably explain our findings [23, 31–33]. Although, the levels were higher in ATN compared to HRS in this study, small sample size limited statistical difference.

Few studies have previously shown association of risk of development of AKI with the Child Turcotte Pugh stage [3, 34]. There is only one study showing association of AKI occurrence

with the baseline MELD score [6]. However, this prospective study examined for in hospital AKI, unlike our study examining one year probability of AKI among LT listed patients. In another prospective study on 92 cirrhosis patients, 82 episodes of AKI occurred. Of 49 patients developing AKI in this study, 33 (67%) developed a second episode of AKI [35], similar to our study. Studies have negative impact of AKI on the outcome of cirrhosis patients and on need for hospitalization, intensive unit care, dialysis, and use of hospital resources, as observed in the current study [1, 5, 6, 9–12]. Small number of patients with documented use of statins in this study limited the analysis of the impact of these drugs on the survival. Of note, use of beta blockers was not associated with the development of AKI risk in this study.

We also examined other biomarkers, which have not been evaluated earlier in patients with cirrhosis such as HE-1, EGF, UMOD or the data are scanty on their assessment such as cystatin C, β2M, OPN, and albumin [36, 37]. HE-1 is a peptide released from endothelial cells resulting in renal vasoconstriction [38]. HE-1 increases in plasma and in urine in HRS patients [39]. In our study, serum and urinary HE-1 levels were highest in HRS followed by ATN and levels were lowest in pre-renal AKI, similar to earlier reports. Cystatin-C, a low molecular weight protein exclusively eliminated by glomerular filtration, has been used for GFR calculation [40]. In one study, plasma cystatin C levels predicted sustained AKI and its outcomes among patients in the intensive care setting [41]. In the current study, there were no differences on urinary cystatin-C levels based on AKI. p2M, a small molecule freely filtered by glomerulus and reabsorbed by proximal tubules, and its serum levels increase with a decline in GFR [42]. In this study, there were no differences on urinary p2M levels as levels may be confounded with infections and inflammatory state. [43] OPN is an inflammatory cytokine, and its serum levels predict onset of AKI and its outcome [44]. In the current study, OPN urinary levels were no different for AKI, likely due to confounding with underlying infections and presence of CKD [45]. Albuminuria is well described as a marker for CKD and for diabetic nephropathy. In the current study, there were no differences on urinary albumin levels based on degree of GFR decline and for AKI.

None of the biomarkers were associated with renal recovery after LT, except for UMOD. In an earlier study, combined model including elevated OPN and tissue inhibitor of metalloproteinase-1, age <57 years, and absence of diabetes was 82% accurate in predicting renal recovery after LT, and this combined model was more accurate compared to models including only biomarkers levels or only clinical variables [46].

Physicians in clinical practice should be extra careful in using diuretics and counseling patients on measures for preventing AKI. This becomes more relevant in the background of shortage of donor kidneys and lack of evidence based guidelines for allocation of SLK transplantation [47, 48]. Whether transjugular intrahepatic portosystemic shunt would be a feasible preventive strategy among cirrhosis patients who have had an episode of AKI remains a testable hypothesis [49].

Analysis of a large homogeneous prospective cohort of cirrhosis patients listed for LT, robust clinical and biomarker data, and use of updated definition of AKI with removal of upper ceiling of 1.5 mg/dL for serum creatinine are strengths of our study. However, our study has

certain limitations including data from a single center, possibility of missing some of the AKI episodes in this retrospective cohort, lack of information on the intravenous albumin use which can confound the MDRD-6 values, and adjudicating cause of AKI based on clinical and laboratory data. Further, information on intra-operative and post-transplant variables which could affect renal function at six months after LT was lacking.

In conclusion, AKI occurs frequently among patients with cirrhosis listed for LT. Development of AKI is associated with increased waitlist mortality and increased use of hospital resources. Patients with AKI who survive without need for transplantation have about 60% probability of developing second episode of AKI within a year from the first episode of AKI. None of the pretransplant biomarkers were associated with recovery of renal function after LT.

We suggest developing larger multicenter studies as a basis for deriving an accurate model combining clinical variables with various biomarkers, to predict recovery of renal function after LT alone. Given encouraging data on the ability of UMOD in predicting renal recovery after LT, studies are suggested to examine proteomics and metabolomics approach on urine samples to explore other biomarkers which could be useful in accurate differentiation of HRS from ATN and in predicting of recovery of renal function after LT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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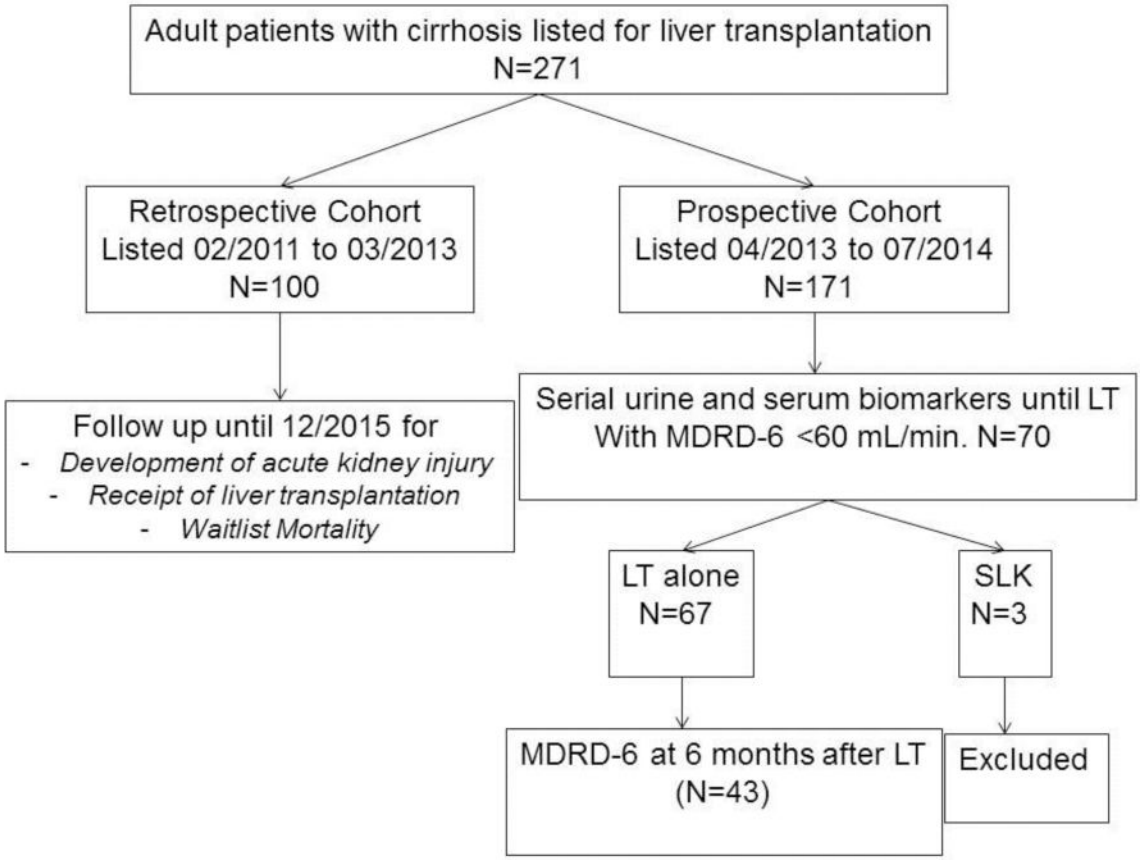

Figure 1.

Study Design and Population

LT: Liver Transplant; AKI: Acute Kidney Injury

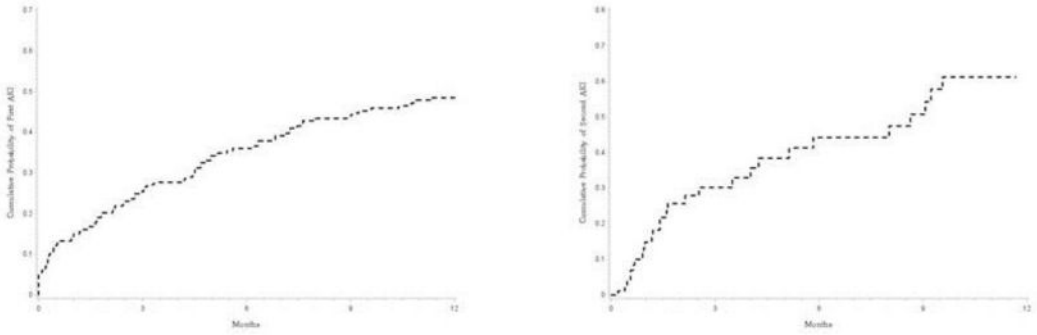

Figure 2.

A) Cumulative probability of development of acute kidney injury at one year from listing for liver transplantation. The results show that the cumulative probability over one year for development of acute kidney injury is about 49% from the time of listing for liver transplantation. B) Cumulative probability of development of second episode of acute kidney injury (AKI) at one year from listing among transplant free survivors of patients with first episode of AKI. Among 45 transplant free survivors of 107 patients with first AKI episode, the cumulative probability of the second episode was about 60% at one year from the time of listing for liver transplantation.

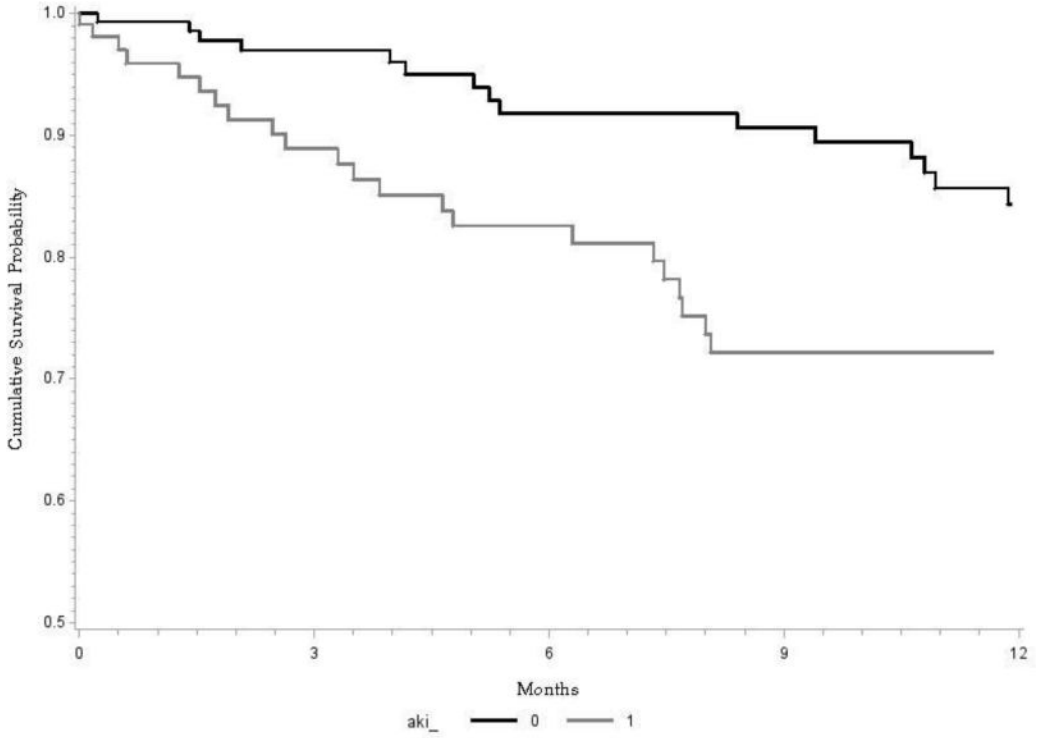

Figure 3.

Kaplan Meier curve showing survival at one year from the time of listing for liver transplantation: Comparison of patients with and without acute kidney injury (AKI). Overall survival was about 86%, significantly lower among patients with AKI compared to those not developing AKI (72.2 vs. 83%, Log Rank P=0.025).

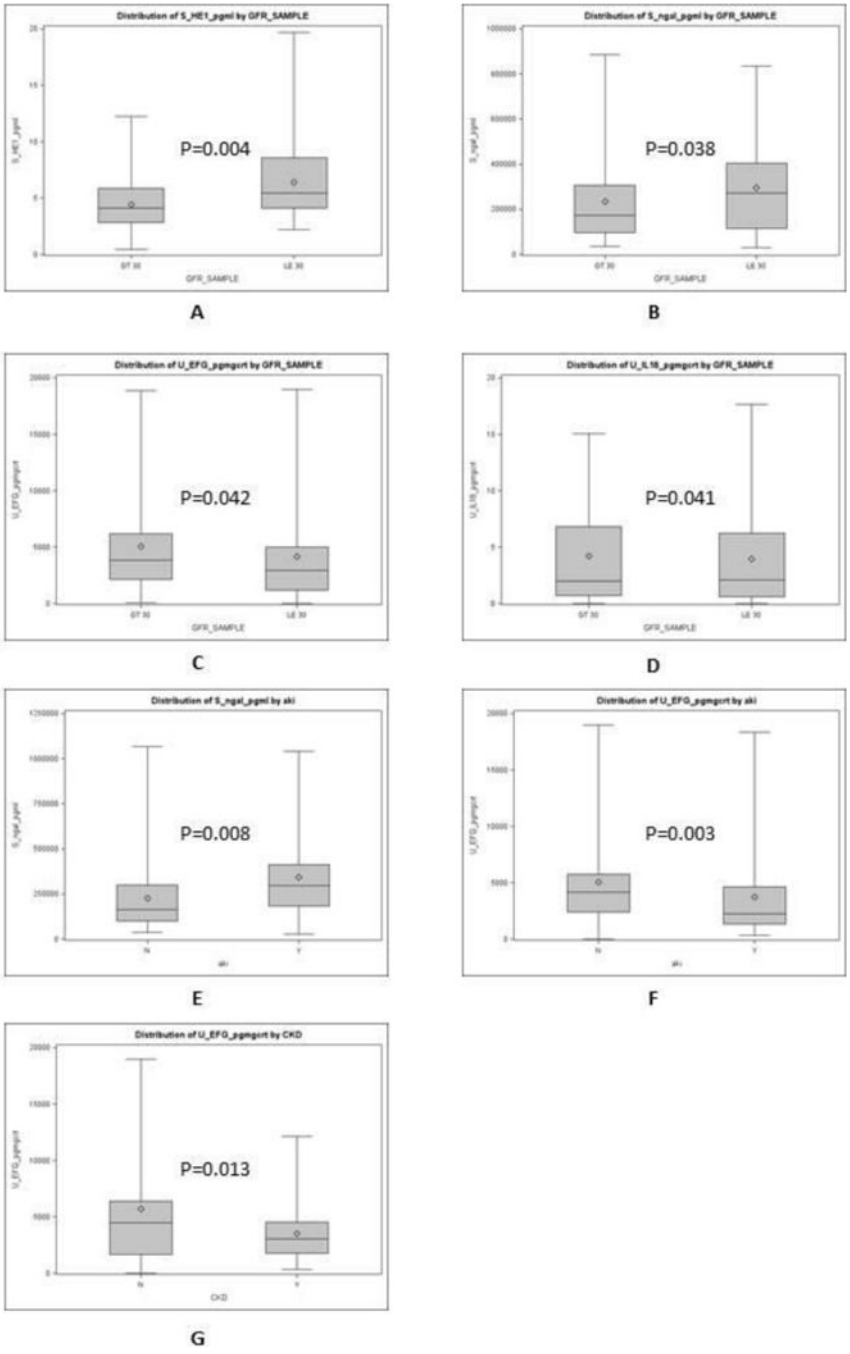

Figure 4.

Box whisker plots comparing samples with modified diet for renal disease-6 (MDRD-6) >30 mL/min vs. samples with MDRD-6 ≤30 mL/min for **A)** serum human endothelin-1 (pg/mL), **B)** serum neutrophil gelatinase associated lipocalin or NGAL, **C)** urinary endothelial growth factor, **D)** urinary interleukin-18 or IL-18; comparing samples without acute kidney injury (AKI) at the time of sample collection vs. samples with AKI for **E)** serum human endothelin-1, **F)** serum neutrophil gelatinase associated lipocalin or NGAL; comparing

samples without chronic kidney disease (CKD) vs. samples with CKD for **G)** urinary endothelial growth factor.

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Table 1

Baseline characteristics at time of listing for liver transplantation

Variable		Total (N=271)	No AKI (N=164)	AKI (N=107)	P
Age in years Median (IQR)		56 (50–62)	57 (51–62)	56 (48–61)	0.064
Males N (%)		170 (63)	106 (65)	64 (60)	0.42
Ethnicity N (%)	Caucasian	226 (83)	140 (85)	86 (80)	
	African American	33 (12)	15 (10)	17 (16)	0.09
	Hispanic	6 (2)	2 (1)	4 (4)	
	Others	6 (2)	6 (4)	0 (0)	
Body mass index Median (IQR)		28 (25–32)	27 (25–32)	28 (25–33)	0.25
Liver disease etiology N (%)	Hepatitis C	100 (37)	62 (38)	38 (35)	
	NASH	72 (27)	40 (24)	32 (30)	0.82
	Alcohol	36 (13)	23 (14)	13 (12)	
	Other	63 (23)	39 (24)	24 (23)	
Beta blockers		143 (53)	88 (54)	55 (51)	0.72
Statins		12 (4.4)	6 (3.7)	6 (5.6)	0.45
Ascites	None	91 (33)	67 (41)	25 (23)	
	Mild to moderate	84 (31)	50 (30)	34 (32)	0.006
	Refractory	95 (36)	47 (29)	48 (45)	
Hepatic encephalopathy		168 (62)	91 (56)	77 (72)	0.008
Varices		170 (63)	101 (62)	69 (64)	0.63
Pre-existing HCC N (%)		56 (21)	41 (25)	15 (14)	0.029
Pre-existing CKD N (%)		64 (24)	27 (16)	37 (35)	0.0006
Platelets $\times 10^9$/L Median (IQR)		73 (55–114)	72 (52–105)	77 (59–127)	0.38
Serum sodium (mEq/L) Median (IQR)		136 (134–139)	137 (134–139)	135 (132–138)	0.01

Variable	Total (N=271)	No AKI (N=164)	AKI (N=107)	P
Listing MELD score Median (IQR)	18 (14–22)	17 (14–19)	19 (15–25)	0.0003
Listing MDRD-6 mL/min Median (IQR)	66 (49–91)	76 (57–101)	56 (37–73)	<0.0001

AKI: Acute kidney injury; IQR: Interquartile range; NASH: Non-Alcoholic Steatohepatitis; HCC: Hepatocellular Carcinoma; CKD: Chronic Kidney Disease; MELD=Model for End-stage Liver Disease; MDRD: Modified Diet in Renal Disease HR: Hazard Ratio; CI: Confidence Interval; CKD: Chronic Kidney Disease; MELD: Model for End-stage Liver Disease

Table 2

Biomarkers levels in serum (pg/ml) and in urine (pg/mg creatinine) comparing samples without vs. with acute kidney injury (AKI) at the time of sample collection.

	No AKI (N=97)				AKI (N=37)				
	N	**Median**	**1st quartile**	**3rd quartile**	**N**	**Median**	**1st quartile**	**3rd quartile**	**P**
Serum Biomarkers									
NGAL	94	162,965	99,213.04	299,049.92	37	297,345.92	182,276.04	411,097.83	0.0083
HE-1	94	4.26	2.64	6.06	37	4.84	2.97	7.84	0.0985
Urine Biomarkers (pg/mg creatinine)									
Albumin	79	3,336,779	764,194	9,085,347	32	7,311,11	2,181,58	13,661,532	0.113
B-2 microglobulin	79	36,874	6,789	190,199	32	19,058	5,886	138,822	0.767
Cystatin C	79	22,754	8,844	78,219	32	20,086	7,971	51,811	0.714
EGF	79	4,253	2,517	6,938	32	2,254	1,350	4,651	0.003
NGAL	79	42,340	12,827	154,712	32	68,020	26,406	188,569	0.154
Osteopontin	79	423,158	187,445	808,137	32	576,900	151,498	937,021	0.527
Uromodulin	79	2,555,037	965,133	5,236,253	32	1,838,723	1,116,396	4,254,726	0.768
Interleukin-18	79	5.87	1.19	26.79	32	3.22	0.73	7.86	0.117
KIM-1	79	1,071	287	2,612	32	1,472	488	3,833	0.304
HE-1	78	0.56	0.20	1.26	31	0.40	0.14	2.38	0.434
FABP-2	44	0.19	0.03	1.69	18	0.13	0.05	0.64	0.896
MDRD-6	85	49	37	68	37	28	22	44	<0.001

NGAL: Neutrophil gelatinase-associated lipocalin; EGF: Epidermal growth factor; KIM: Kidney injury molecule; HE: Human endothelin; FABP: Fatty acid binding protein; MDRD: Modified diet for renal disease

Table 3

Biomarkers levels in serum (pg/ml) and in urine (pg/mg creatinine) samples comparing types of acute kidney injury (AKI): pre-renal volume responsive vs. acute tubular necrosis (ATN) vs. hepatorenal syndrome (HRS).

	Pre-renal AKI (N=22)				ATN (N=3)				HRS (N=12)			
	N	**Median**	**1st quartile**	**3rd quartile**	**N**	**Median**	**1st quartile**	**3rd quartile**	**N**	**Median**	**1st quartile**	**3rd quartile**
Serum Biomarkers												
NGAL	22	238,095	163,881	357,090	3	382,541	339,747	836,177	12	296,290	182,991	587,019
HE-1	22	4.35	2.85	7.43	3	2.88	2.65	19.66	12	6.61	4.61	9.47
Urine Biomarkers (pg/mg creatinine)												
Albumin	19	3,895,366	1,583,940	13,132,606	2	16,522,643	14,649,559	18,395,725	11	7,657,418	1,127,192	13,173,988
B-2 microglobulin	19	29,273	4,228	143,138	2	886,027	13,946	1,758,108	11	18,364	6,081	134,507
Cystatin C	19	20,934	8,417	37,098	2	93,026	9,606	176,446	11	15,231	6,961	329,438
EGF	19	2,943	1,765	4,983	2	1,316	1,040	1,591	11	1,328	913	4,837
NGAL	19	47,893	38,437	207,814	2	607,849	598,718	616,980	11	67,078	9,266	149,689
Osteopontin	19	760,531	429,939	1,096,634	2	166,367	96,446	236,289	11	153,846	87,863	580,297
Uromodulin	19	2,803,694	1,697,890	4,951,781	2	1,147,485	893,124	1,401,845	11	1,138,358	823,544	2,638,723
Interleukin-18	19	3.36	0.74	8.55	2	4.96	3.09	6.83	11	2.74	0.43	9.36
KIM-1	19	1,511	507	4,036	2	3,607	3,167	4,047	11	934	149	1,896
HE-1	19	0.31	0.09	2.38	2	1.50	0.40	2.60	10	0.39	0.17	1.24
FABP-2	9	0.08	0.03	0.64	2	0.10	0.07	0.14	7	0.48	0.05	11.81
MDRD-6	22	35	27	51	3	19	13	19	12	23	18	30

NGAL: Neutrophil gelatonase-associated lipocalin; EGF: Epidermal growth factor; KIM: Kidney injury molecule; HE: Human endothelin; FABP: Fatty acid binding protein; MDRD: Modified diet for renal disease

Table 4

Biomarkers levels in serum (pg/ml) and in urine (pg/mg creatinine) samples taken within one month prior to liver transplantation (LT) alone among patients with pre-transplant MDRD <30 mL/min: comparing without vs. with recovery of renal function at six months after LT (MDRD-6 >50 mL/min)

	No Recovery (N=10)				Recovery (N=5)				
	N	**Median**	**1st quartile**	**3rd quartile**	**N**	**Median**	**1st quartile**	**3rd quartile**	**P**
Serum Biomarkers									
NGAL	7	183,707	113,572	299,018	5	411,098	293,614	663,551	0.220
HE-1	7	6.19	4.13	7.84	5	9.11	4.84	9.82	0.529
Urine Biomarkers (pg/mg creatinine)									
Albumin	7	9,070,194	3,046,796	40,272,481	5	6,964,801	2,830,440	11,851,111	0.723
B-2 microglobulin	7	15,253	8,417	6,036,864	5	18,364	3,467	122,286	0.723
Cystatin C	7	175,206	13,967	396,264	5	39,080	15,231	186,934	0.906
EGF	7	4,684	2,848	4,920	5	1,151	344	1,328	0.302
NGAL	7	59,420	28,723	113,169	5	149,689	68,962	179,275	0.416
Osteopontin	7	540,697	304,619	1,092,702	5	129,306	87,863	153,846	0.215
Uromodulin	7	5,248,257	2,762,422	9,280,816	5	823,544	265,520	1,823,135	0.104
Interleukin-18	7	4.90	1.99	7.59	5	6.67	2.74	8.55	0.723
KIM-1	7	2,340	1,022	3,346	5	1,838	813	6,458	0.906
HE-1	7	2.07	0.19	4.13	5	0.34	0.14	0.45	0.416
FABP-2	7	33.82	1.39	66.24	5	0.50	0.31	6.16	0.299
MDRD-6 Pre Transplant	7	28	16	40	5	21	19	27	0.636

NGAL: Neutrophil gelatinase-associated lipocalin; EGF: Epidermal growth factor; KIM: Kidney injury molecule; HE: Human endothelin; FABP: Fatty acid binding protein; MDRD: Modified diet for renal disease